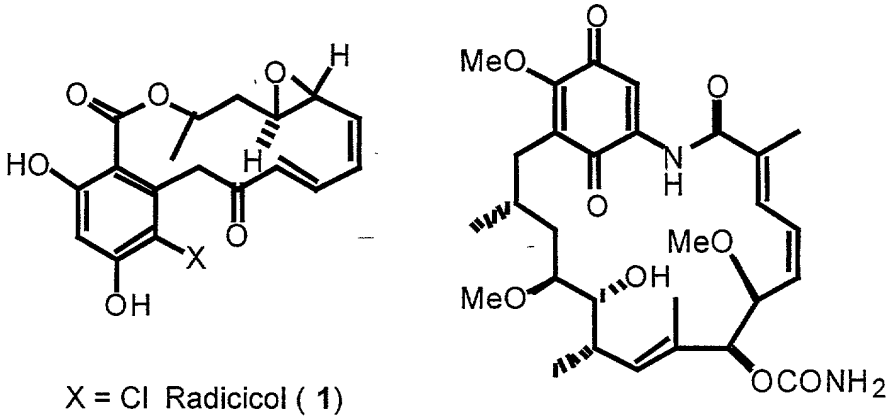
Figure 1. Structures of Monocillin I, Radicicol and Geldanamycin



X = Cl Radicicol (**1**)
X = H Monocillin I (**2**)

Geldanamycin (**3**)

Figure 1

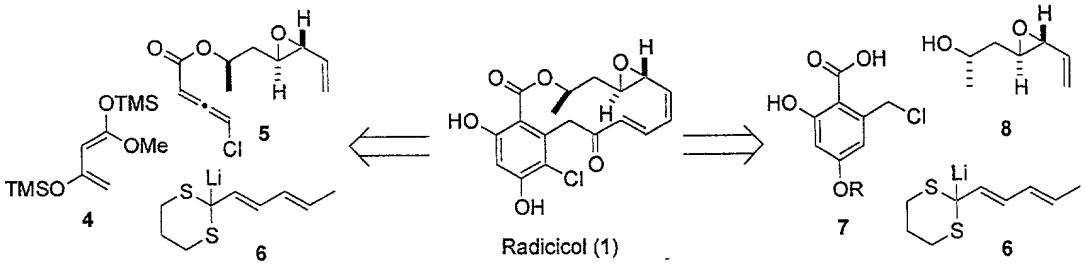
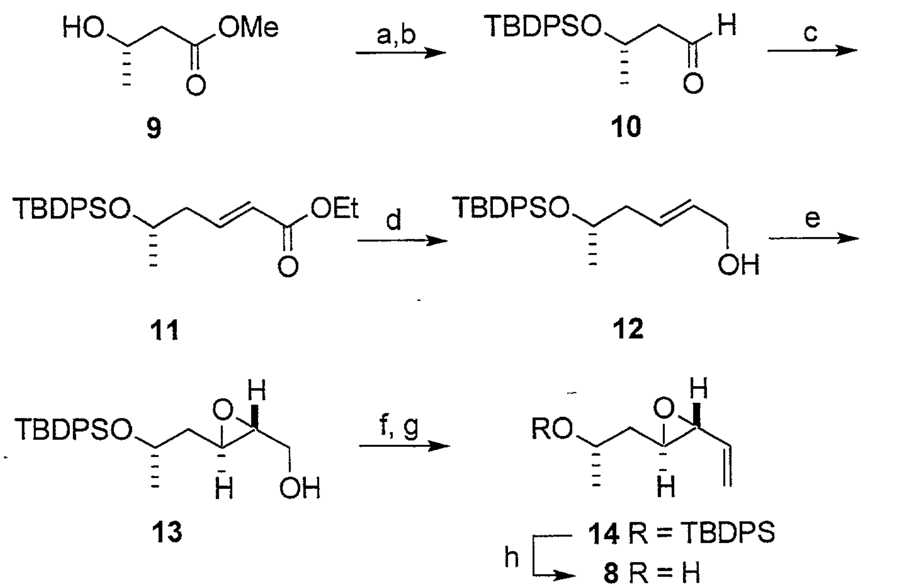

OTMS
OMe
TMSO
4
5
Cl
Li
S
S
6
HO
O
O
H
Cl
OH
Radicicol (1)
OH
HO
Cl
OR
7
8
6

Figure 2



(a) TBDPSCl, imid., >95%; (b) DIBAL-H, –78 °C, 92%; (c) LiCl, DIPEA $(EtO)_2P(O)CH_2CO_2Et$, 95%; (d) DIBAL-H, –20 °C, 96%; (e) (+)-DET, $Ti(OiPr_4)$, TBHP, 90%, >95% ee; (f) SO_3•pyridine, Et_3N, DMSO, 90%; (g) Ph_3PCH_3Br, NaHMDS, 0 °C, 82%; (h) TBAF, 89%.

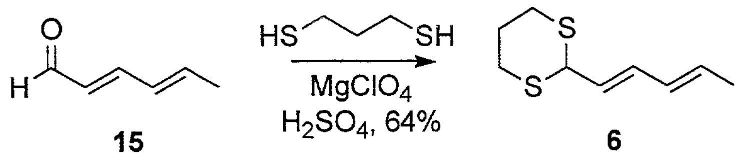
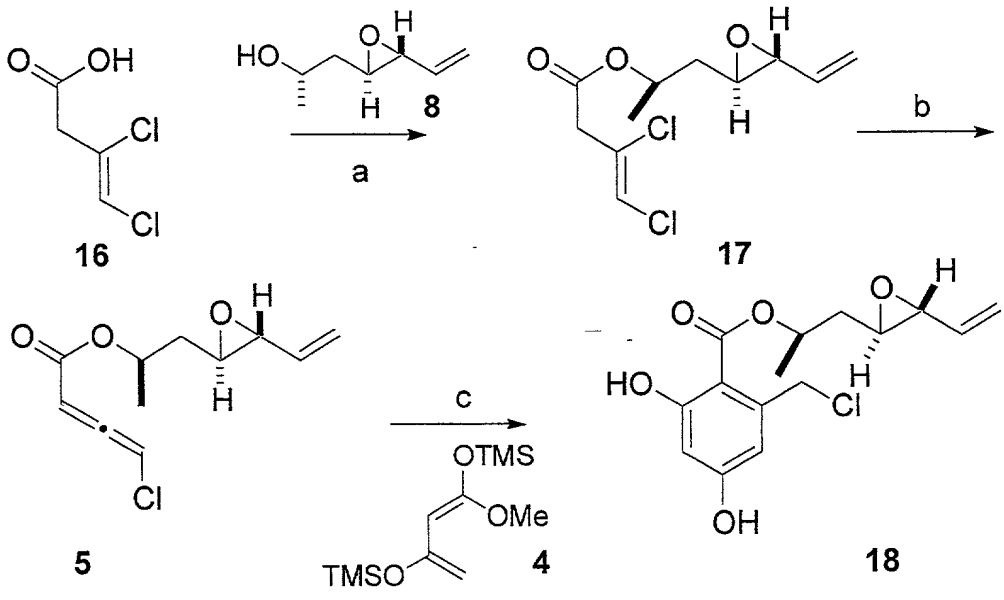


Figure 3



a. DEAD, PPh_3, 70%; b. iPr_2NEt, 70%; c. 50% (4:1)

Figure 4

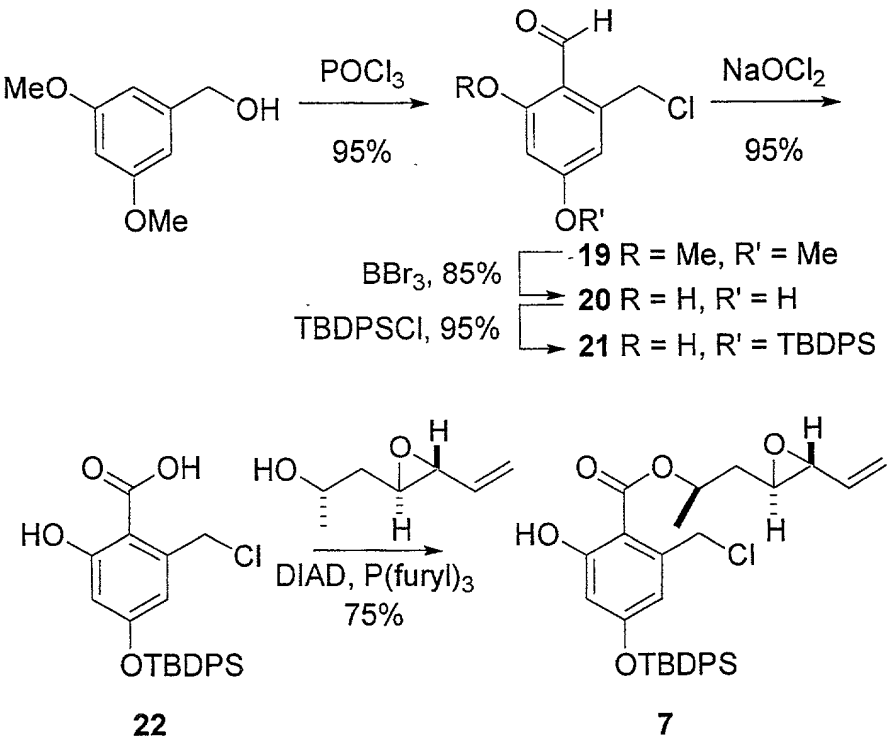
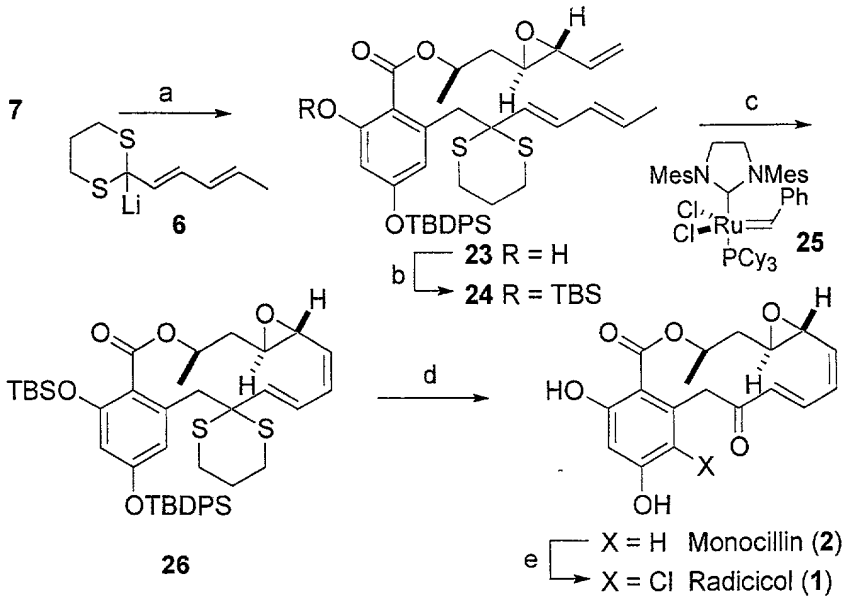

MeO
OH
OMe
POCl3
95%
O
H
RO
Cl
OR'
NaOCl2
95%
BBr3, 85%
TBDPSCl, 95%
19 R = Me, R' = Me
20 R = H, R' = H
21 R = H, R' = TBDPS
O
OH
HO
Cl
OTBDPS
22
HO
O
H
H
DIAD, P(furyl)3
75%
O
O
HO
Cl
OTBDPS
7

Figure 5



a. *n*-BuLi, –78° C, 50% (6:1); b. TBSCl, 83%; c. 42 °C, 70%; d. (i) mCPBA, (ii) Ac_2O, Et_3N, H_2O, 60°C, (iii) $NaHCO_3$, MeOH, 60%; e. SO_2Cl_2, 50%

Figure 6

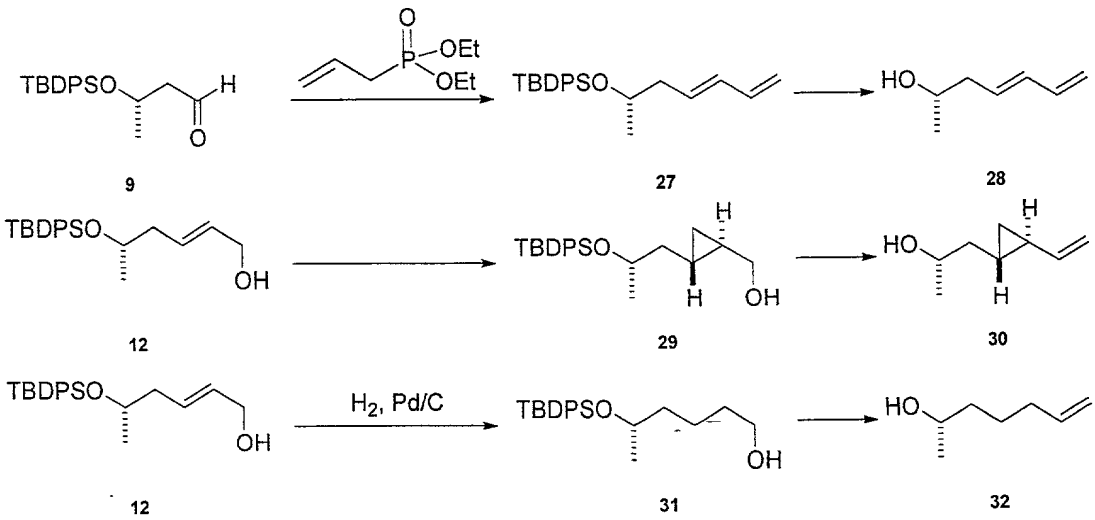
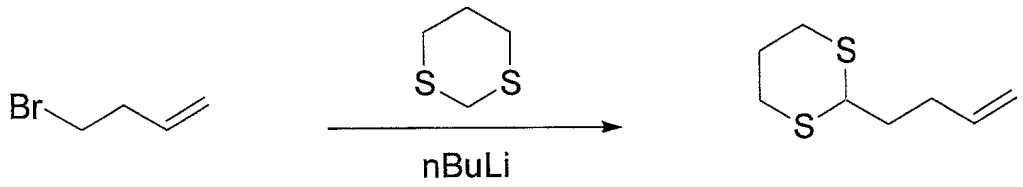


Figure 7



33

34

Figure 8

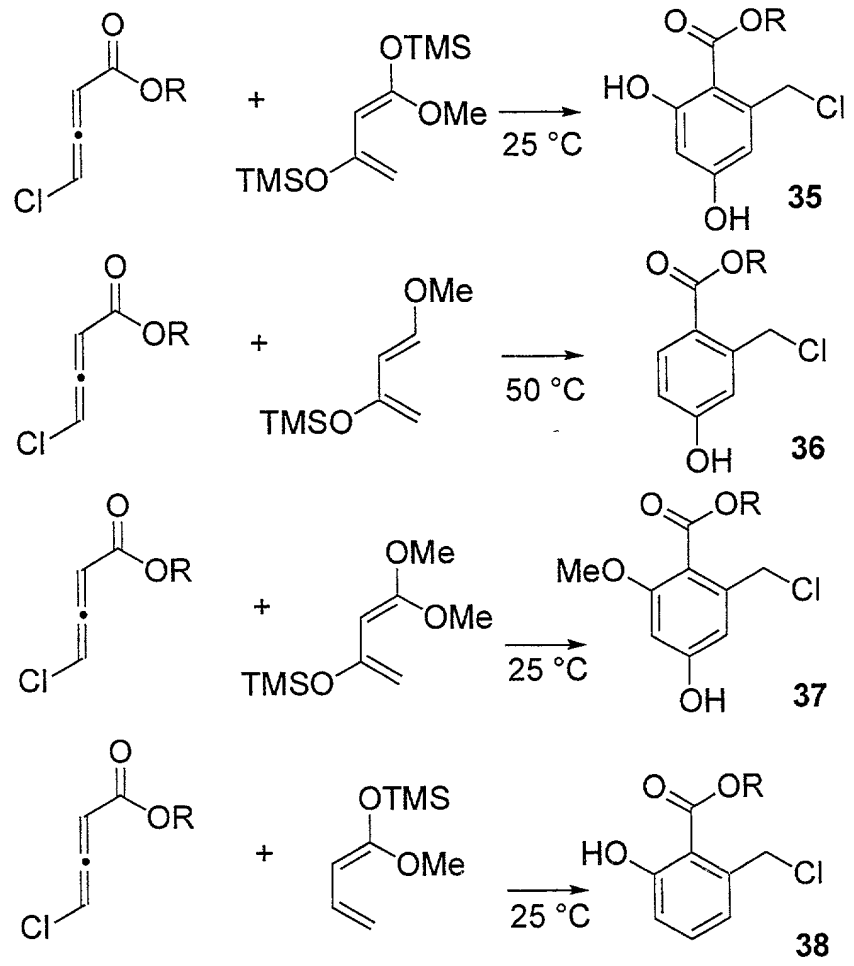
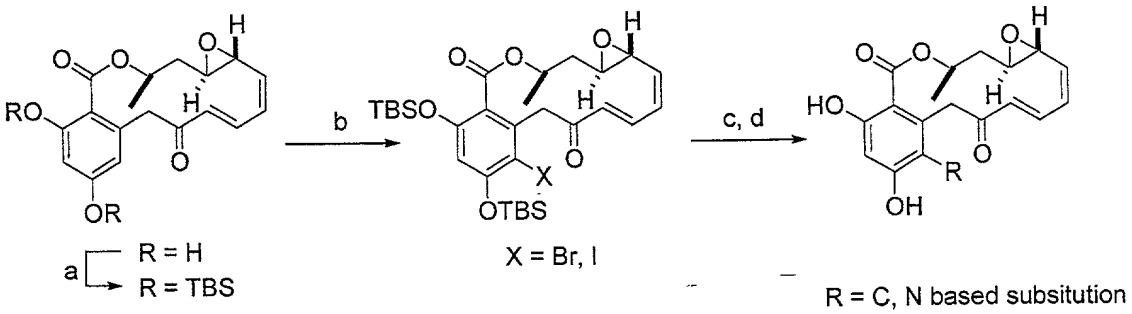


Figure 9

Generation of Diversity at Aromatic Positions



a. TBSCl, pyridine; b. NIS or NBS, TsOH; c. $Pd(PPh)_3$, $RSnBu_3$; d. nBu_4NF

Figure 10

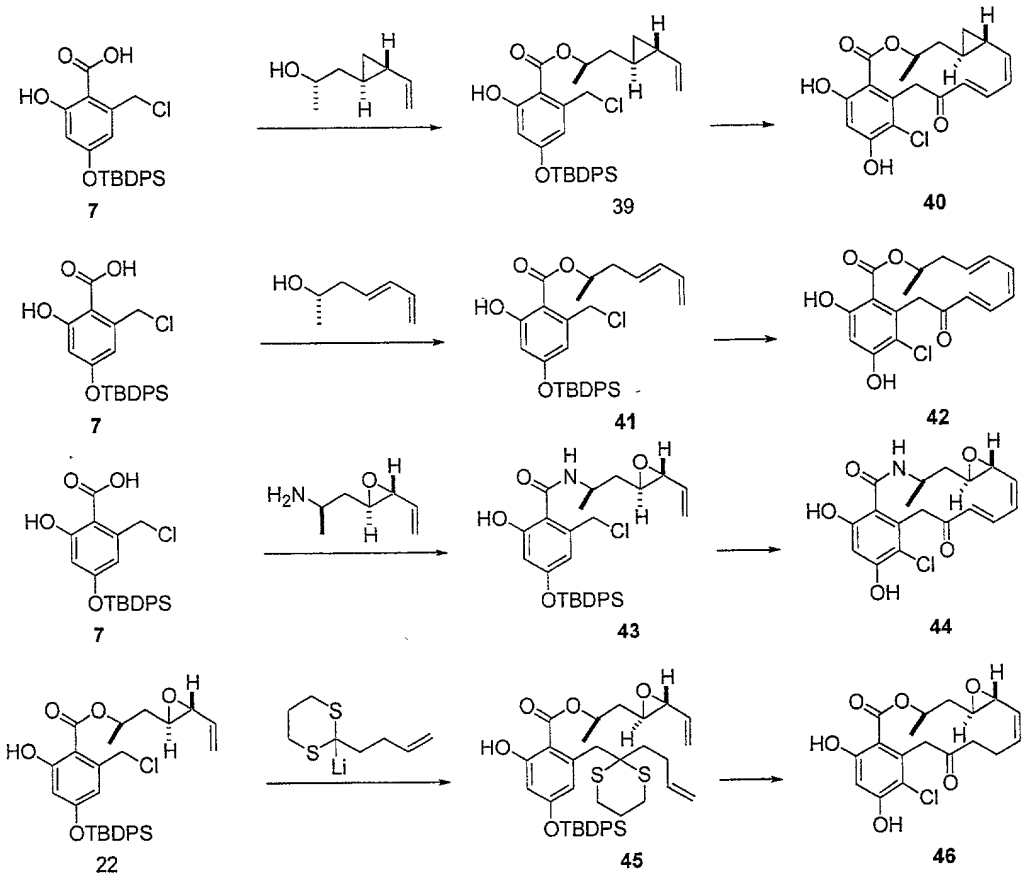


Figure 11

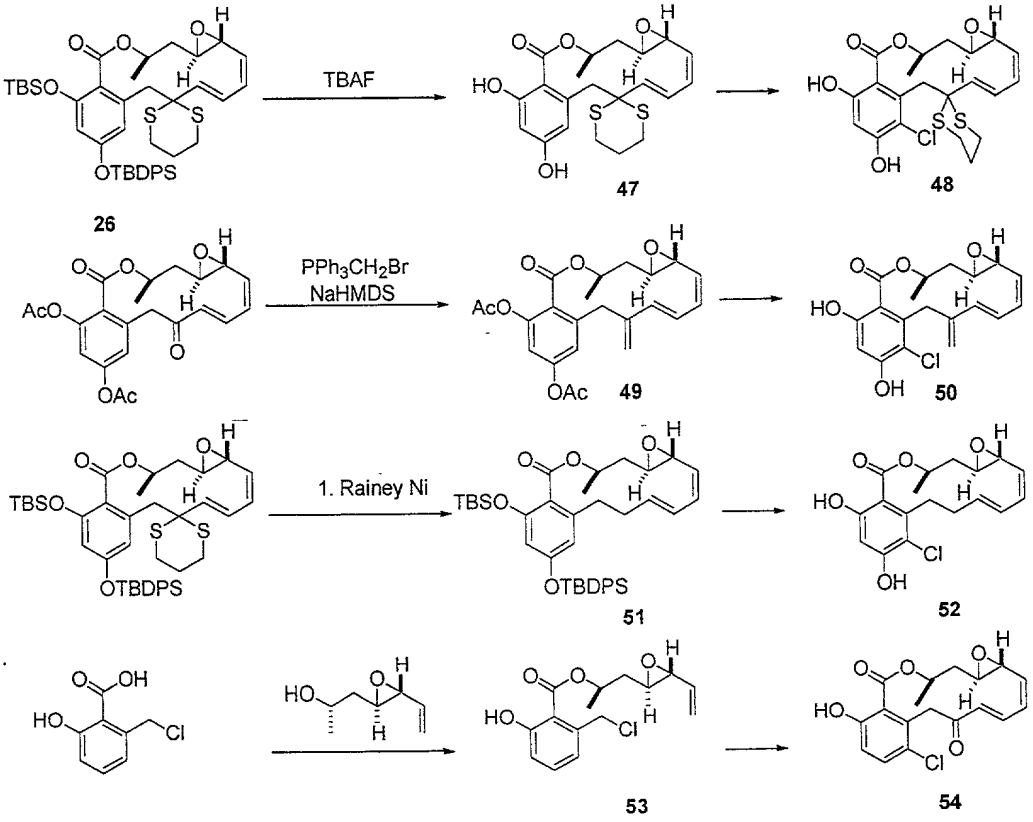
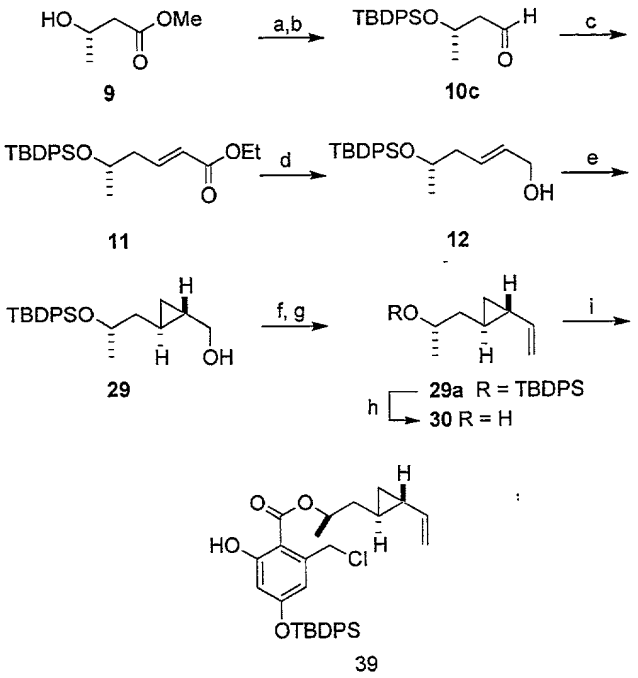
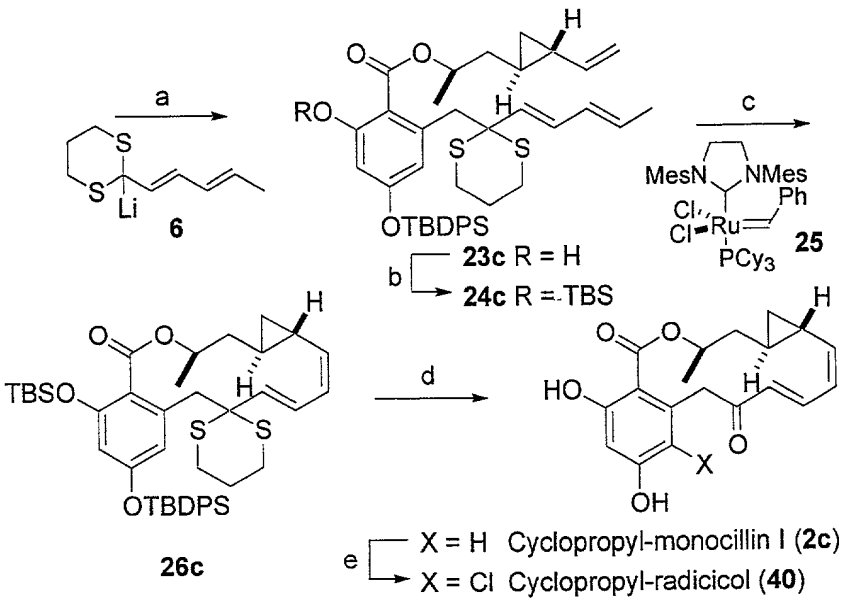

TBSO
OTBDPS
26
TBAF
HO
OH
47
Cl
48
AcO
OAc
PPh_3CH_2Br
NaHMDS
49
50
1. Rainey Ni
51
52
53
54

Figure 12



[a] (a) TBDPSCl, imid., >95%; (b) DIBAL-H, –78 °C, 92%; (c) LiCl, DIPEA $(EtO)_2P(O)CH_2CO_2Et$, 95%; (d) DIBAL-H, –20 °C, 96%; (e) (+)-tetramethyltartaricacid diamide-BBu, Et_2Zn, CH_2I_2, 9 >95% ee; (f) SO_3•pyridine, Et_3N, DMSO, 90%; (g) Ph_3PCH NaHMDS, 0 °C, 82%; (h) TBAF, 89%; (i) 7 , $P(furyl)_3$, DIA benzene, 60%

Figure 13



a. *n*-BuLi, –78° C, 75% (3:1); b. TBSCl, 83%; c. 42 °C, 20%; d. (i) mCPBA, (ii) Ac_2O, Et_3N, H_2O, 60°C, (iii) $NaHCO_3$, MeOH, 60%; e. SO_2Cl_2, 80%

Figure 14

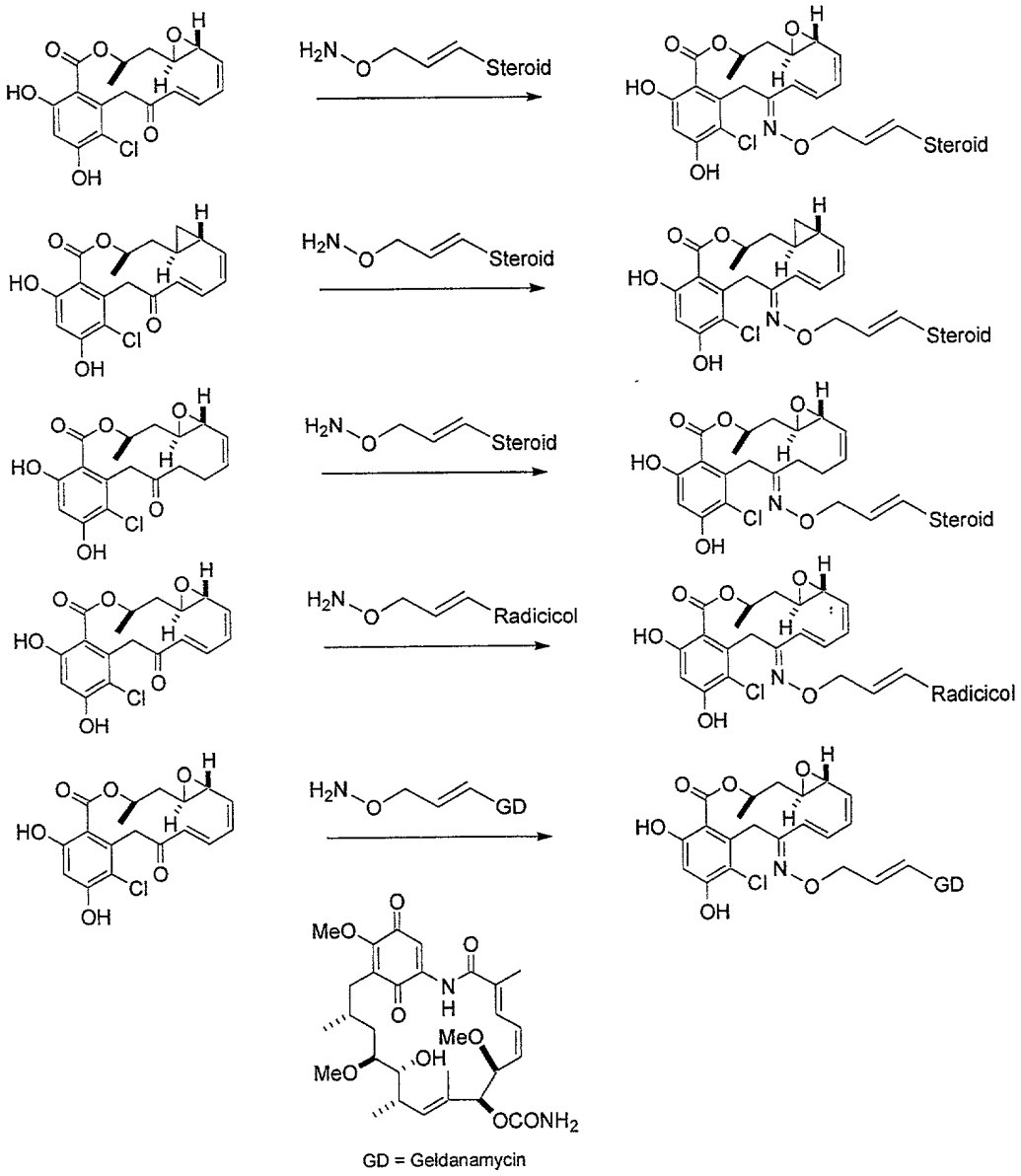


Figure 15

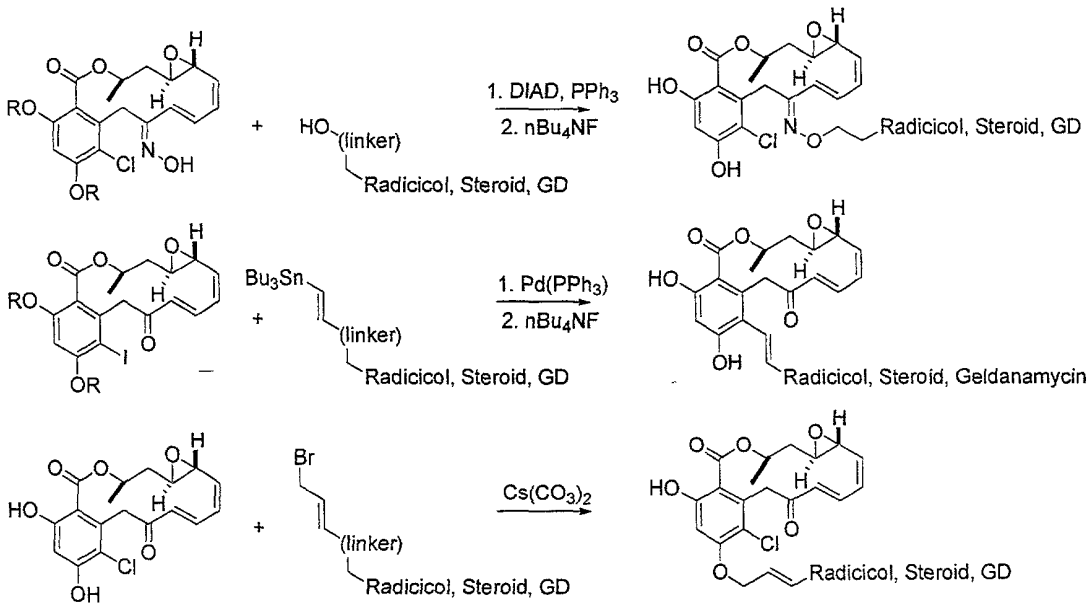
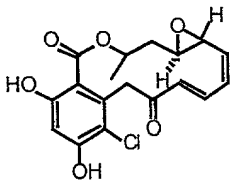
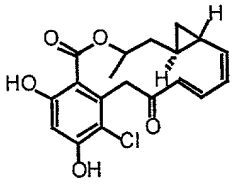

1. DIAD, PPh3
2. nBu4NF
HO (linker) Radicicol, Steroid, GD
Radicicol, Steroid, GD
1. Pd(PPh3)
2. nBu4NF
Bu3Sn (linker) Radicicol, Steroid, GD
Radicicol, Steroid, Geldanamycin
Cs(CO3)2
Br (linker) Radicicol, Steroid, GD
Radicicol, Steroid, GD

Figure 16

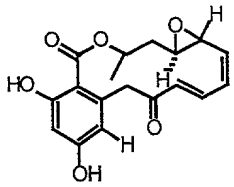
I. Radicicol



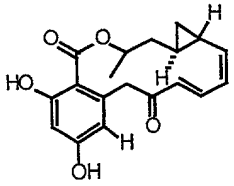
III. Cyclopropyl radicicol



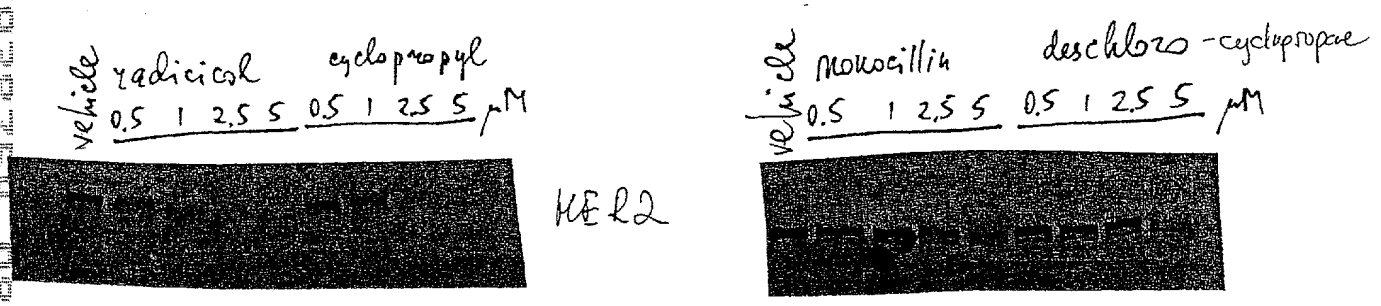
II. Monocillin I



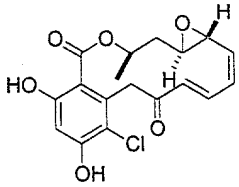
IV: Cyclopropyl monocillin



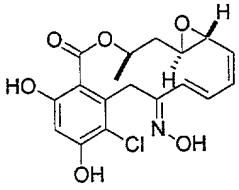
MCF7 Cells Treated with Radicicol and Analogues



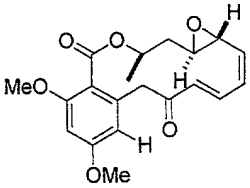
I. Radicicol



VII. Radicicol Oxime



V. Dimethyl Monocillin I



VI. Dimethyl Radicicol

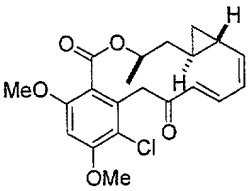
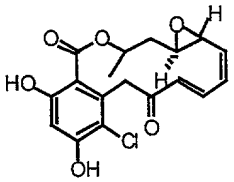
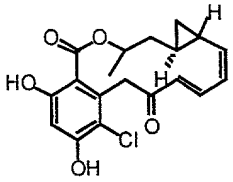


Figure 17

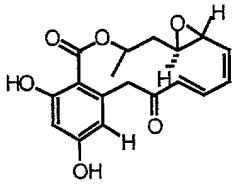
I. Radicicol



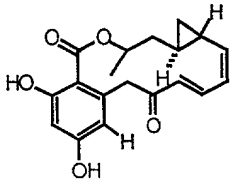
III. Cyclopropyl radicicol



II. Monocillin I



IV: Cyclopropyl monocillin



BT474 Cells Treated with Novel Radicicols (24 hrs.)

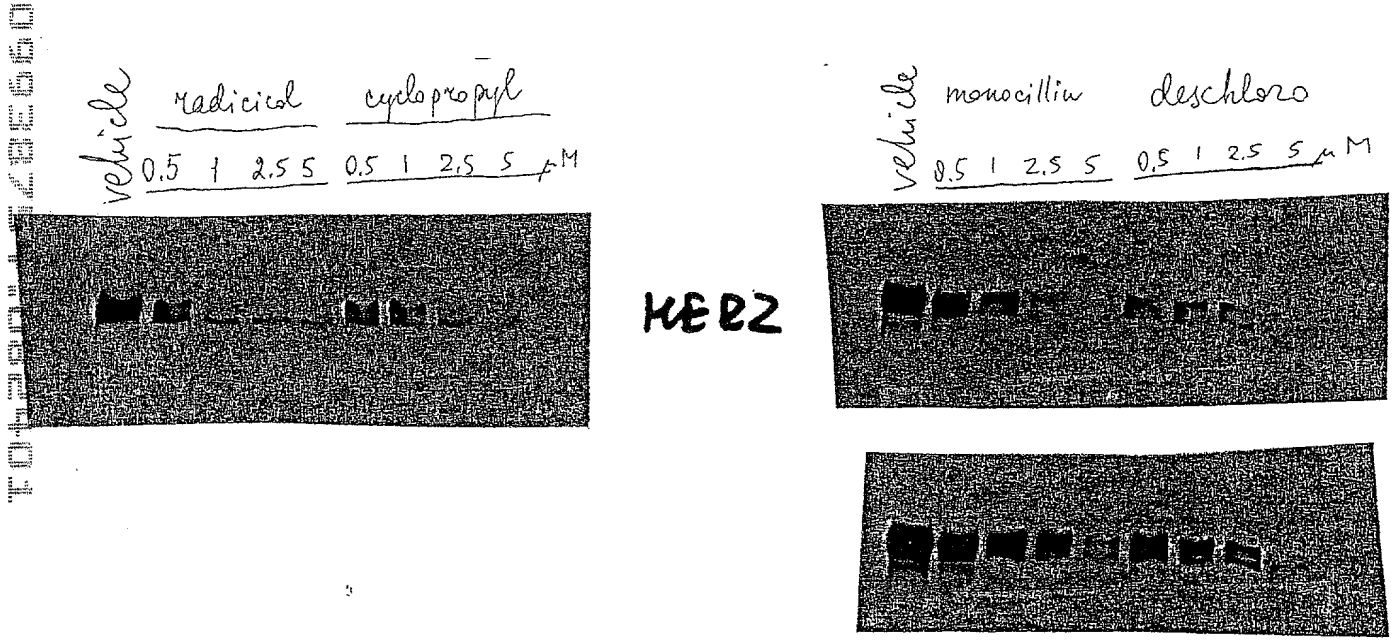


Figure 18

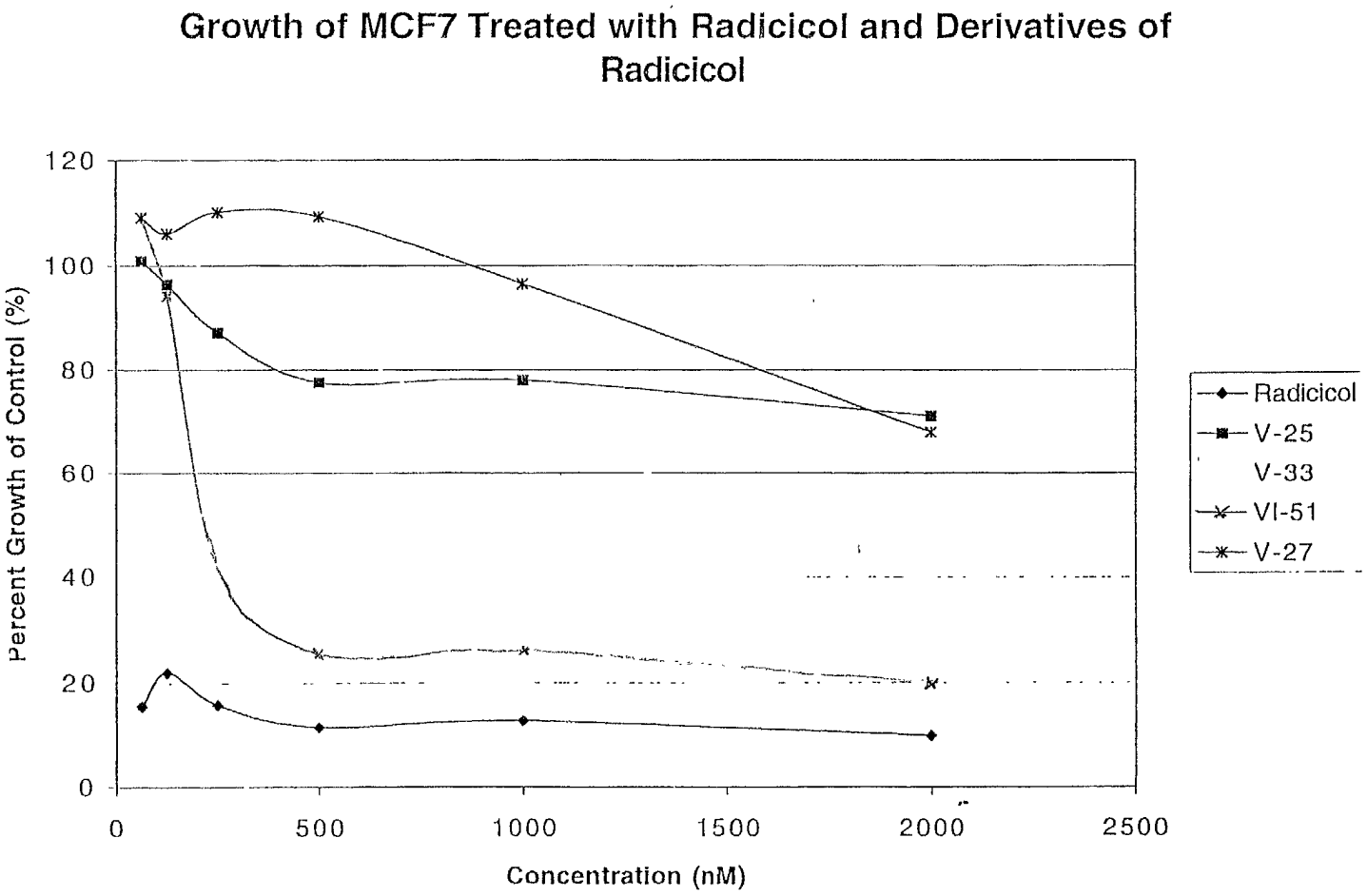

Growth of MCF7 Treated with Radicicol and Derivatives of Radicicol
Percent Growth of Control (%)
120
100
80
60
40
20
0
0
500
1000
1500
2000
2500
Concentration (nM)
Radicicol
V-25
V-33
VI-51
V-27

Figure 19

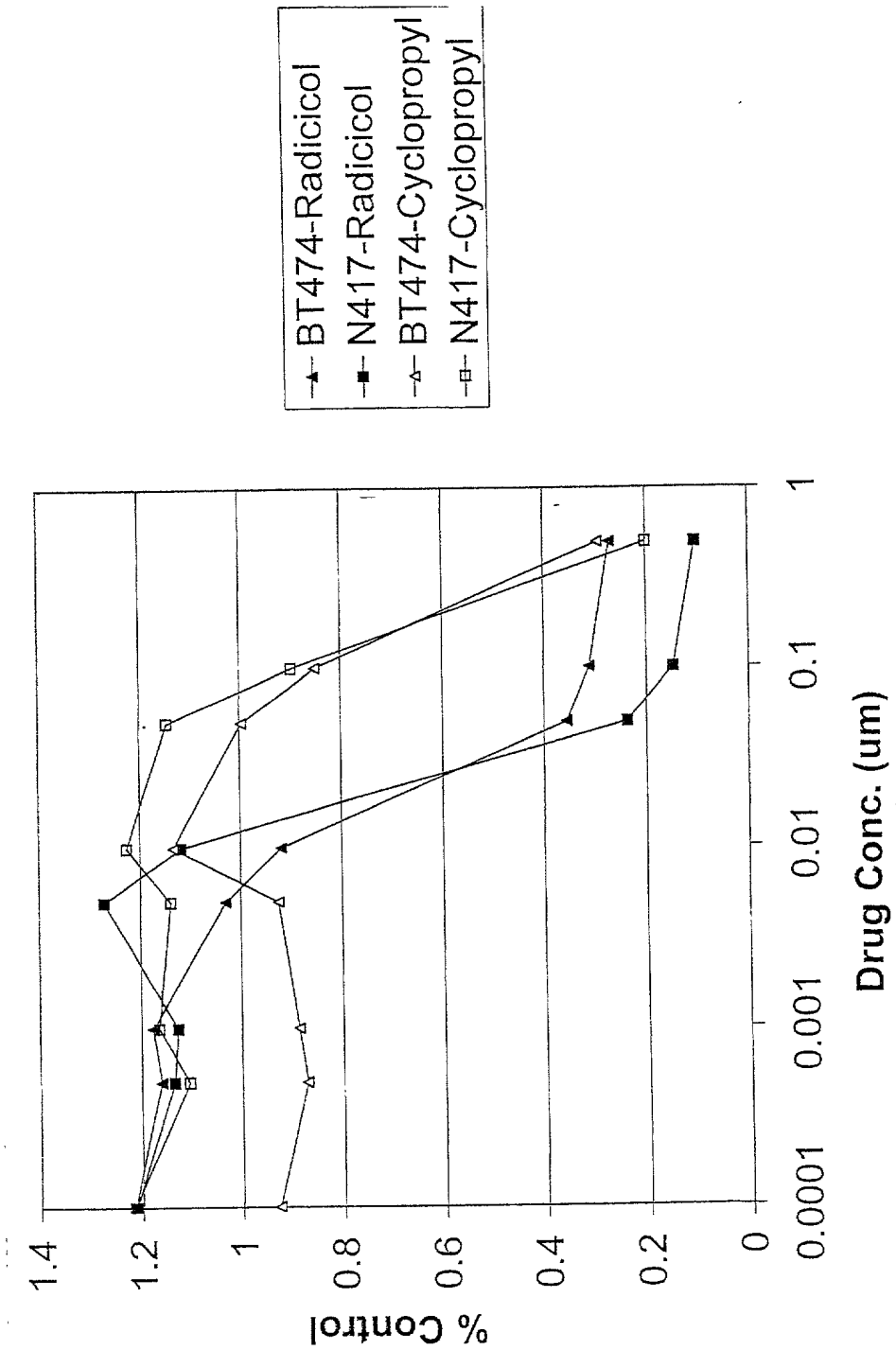

BT474-Radicicol
N417-Radicicol
BT474-Cyclopropyl
N417-Cyclopropyl
% Control
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.0001
0.001
0.01
0.1
1
Drug Conc. (um)

Figure 20

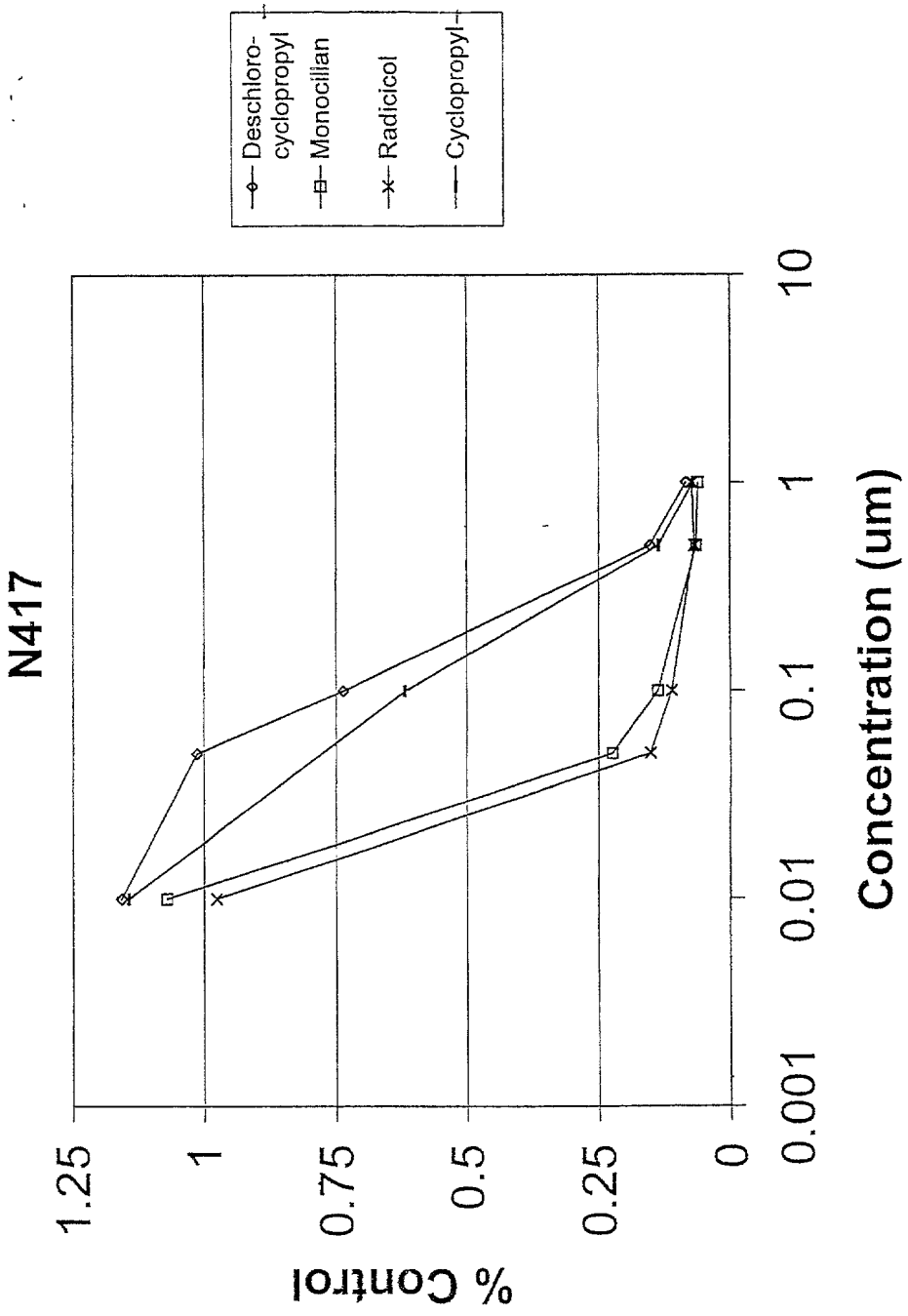

N417
% Control
1.25
1
0.75
0.5
0.25
0
0.001
0.01
0.1
1
10
Concentration (um)
Deschloro-cyclopropyl
Monocilian
Radicicol
Cyclopropyl

Figure 21